NHS Grampian

NHS Grampian Staff Guidelines For The Early In-Hospital Pharmacological Management Of Unstable Angina And Non-ST-Segment-Elevation Myocardial Infarction Patients (17 Years And Older)

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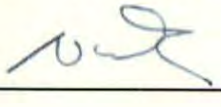
Policy Statement:
It is the responsibility of all staff to ensure that they are working to the most up to date and relevant guideline, policies, protocols and procedures.

Version 5

Executive Sign-Off

This document has been endorsed by the Medical Director of NHS Grampian

Signature: 

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1. Introduction

This document details the suggested initial in-hospital pharmacological management of patients within NHS Grampian who present with a working diagnosis of unstable angina (UA) or non-ST-segment-elevation myocardial infarction (NSTEMI).

1.1. Objectives

To ensure the uniform, safe and effective pharmacological management of patients with a working diagnosis of UA/NSTEMI across NHS Grampian.

1.2. Clinical Situations

Patients with a diagnosis or suspected diagnosis of UA/NSTEMI (see reference 2 for guidance on diagnosis if needed, or consult a senior clinician). Please note this document is not intended to facilitate the diagnosis.

1.3. Patient Groups to Which This Document Applies

This document applies to all patients in NHS Grampian who are 17 years of age or above and have a current working diagnosis of an UA/NSTEMI, unless any treatment is contraindicated. See relevant Summary of Product Characteristics (SmPC) (1) for each medicine.

1.4. Patient Groups to Which This Document Does Not Apply

This document does not apply to children (aged 16 and below), those who have a contraindication to the suggested treatments, e.g. Creatinine Clearance (CrCl) <20mL/min, or for whom the enteral route is not available/suitable, e.g. intubated patients without enteral tube access. See relevant SmPC (1) for each medicine.

STEMI (ST-segment Elevation Myocardial Infarction) patients are not covered by this guideline and should be referred to the Coronary Care Unit (CCU) Decision Support or the cardiac cath lab for consideration of primary percutaneous coronary intervention (PCI). If thrombolysis is appropriate to be administered (after discussion with a cardiologist) then dalteparin (**not** fondaparinux) should be used in these patients (please contact CCU for thrombolysis and dalteparin administration guidance).

2. Early In-Hospital Management of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction

(Summarised in Appendix 2: Flowchart: in-hospital management of UA/NSTEMI)

This guideline has been developed to clarify the initial pharmacological management of UA and NSTEMI, with particular focus on the role of fondaparinux (Appendix 1) and ticagrelor, and it is applicable to all medical and surgical wards across NHS Grampian.

If a diagnosis of UA/NSTEMI is suspected, standard in-hospital treatment is immediate administration of dual antiplatelet therapy (aspirin plus ticagrelor/clopidogrel) and parenteral anticoagulant therapy (dalteparin or fondaparinux) if early invasive management of the acute coronary syndrome (ACS) is not planned.

The strategy for invasive management should be discussed and agreed with a cardiology consultant or specialist registrar if it is felt that an early invasive strategy is warranted. The cardiologist will then advise on antiplatelet treatment or arrange for administration of such medications on arrival at the cardiac cath lab.

The European Society of Cardiology Guidance on the Management of Acute Coronary Syndromes 2023 and the Scottish Intercollegiate Guidelines Network (SIGN) Guidance 148: Acute Coronary Syndromes (April 2016) recommends that ticagrelor be used in preference to clopidogrel [2, 3] unless the risk (bleeding) outweighs the benefit (reduction in recurrent thrombotic events).

Ticagrelor belongs to a novel chemical class, cyclopentyl triazolopyrimidine and is an oral, reversibly binding P2Y12 adenosine diphosphate receptor antagonist with a plasma half-life of 12 hours. Ticagrelor has a more rapid and consistent onset of action compared with clopidogrel, but additionally it has a quicker offset of action so that recovery of platelet function is faster [2, 3].

Ticagrelor is associated with AV block, bradycardia and episodes of ventricular standstill [1]. It is therefore not recommended to be used in patients with bradycardia or any form of heart block. Clopidogrel should be considered as an alternative in these patients (dosing as below).

Fondaparinux (Appendix 1) is recommended in the current SIGN [2], European Society of Cardiology [3] and NICE [5] guidelines, and is associated with a lower risk of bleeding than low molecular weight heparins [6]. All guidelines recommend that fondaparinux has the most favourable efficacy-safety profile for the management of ACS. It also has a simpler dosing regimen, 2.5mg given once daily regardless of the patient's weight.

It should be noted that fondaparinux cannot be used as a bridge for anticoagulants in those with active thrombus or at high risk of developing thrombi (as well as those with mechanical prosthetic heart valve replacements and antiphospholipid syndrome amongst other indications), and that recommendations on timing of initiation of parenteral anticoagulation vary dependent on the oral anticoagulant it will be

replacing (see individual SmPC for oral anticoagulant agents and/or discuss with pharmacy/senior medical staff). Dalteparin (or unfractionated heparin continuous infusion) may be preferred over fondaparinux in these situations. For dosing recommendations for dalteparin in NSTEMI/UA, see SmPC (http://www.medicines.org.uk/emc/medicine/26901) or dosing table on CCU intranet pages.

Ticagrelor is not recommended to be prescribed in combination with anticoagulants, and patients who require an anticoagulant (e.g. warfarin, apixaban, rivaroxaban, dabigatran or edoxaban) to continue post ACS should receive clopidogrel rather than ticagrelor [2, 3]. Careful consideration should be made to the continued use of dual antiplatelet treatment with an anticoagulant. This should only be done where the benefit outweighs the increased risk of bleeding and for the shortest duration possible, using the combination with the lowest bleeding risk. Guidance on appropriate duration of therapies in different situations can be found in the ESC Guidance, or advice sought from a cardiologist [2, 4].

If clopidogrel is deemed most suitable for use, a loading dose of at least 300mg, but ideally 600mg (note this dose is unlicensed but recommended particularly if the patient is likely to proceed to angiogram and PCI), should be administered as a once only dose, then continued at 75mg once daily for the defined duration.

Generally, if the patient is to be taken for cardiac angiography, an oral anticoagulant [DOAC (Direct Oral Anticoagulant) or vitamin K antagonist] would be replaced with injectable anticoagulation to cover its effects (usually subcutaneous dalteparin – see dosing tables on CCU intranet page for ACS dosing – or intravenous heparin – see AMIA intranet page for prescribing protocol), and aspirin and clopidogrel prescribed (loading and maintenance dosing). Please follow appropriate advice within the SmPC of individual products for switching between oral and injectable agents. [Note: if alternative IV/sc anticoagulation is used, fondaparinux should not be concurrently prescribed]. Current recommendations if the patient proceeds to PCI [2] include aspirin for 7-30 days (depending on ischaemic vs bleeding risk) with clopidogrel for 12 months alongside continued oral anticoagulant. The recommendation for 'triple therapy' (aspirin plus clopidogrel plus an oral anticoagulant) at discharge should be made by senior cardiology staff (this is usually communicated on the angiogram report). Patients who require 'triple therapy' should have consideration given to an appropriate duration of GI (gastrointestinal) protection.

For patients who are not deemed appropriate for cardiac angiography, a widely accepted approach is to continue the oral anticoagulant (DOAC or vitamin K antagonist) and add clopidogrel monotherapy for between 3 and 12 months [2], depending on bleeding risk (and with consideration of appropriate mitigating factors, such as GI protection).

It is recommended that after a NSTEMI patients should receive up to 12 months of dual antiplatelet therapy [2], although there may be clinical reasons why a shorter duration is recommended (on the advice of a Consultant Cardiologist).

2.1. Initial pharmacological management of UA/NSTEMI patients in whom early invasive management (PCI or CABG within 24 hours) is not planned.

At initial presentation (unless contraindicated*):

- Aspirin 300mg once only (do **NOT** give if already administered in community).
- **PLUS** ticagrelor 180mg once only loading dose.
- Followed by ticagrelor 90mg twice daily. The second dose of ticagrelor (90mg) should be administered 6 to 18 hours after the loading dose.
- Fondaparinux 2.5mg subcutaneously (s/c)** also administered at initial presentation.

In those for whom ticagrelor is not advised (e.g. those with heart block, high bleeding risk or requirement for concurrent anticoagulation):

- Clopidogrel, at least 300mg (but ideally 600mg if planned for angiography out with initial 24 hours) as a once off loading dose, followed by 75mg once daily thereafter.

Continuing treatment (unless contraindicated*):

- Aspirin 75mg once daily to be continued indefinitely***.
- Ticagrelor 90mg twice daily to continue for up to 1 year.
- Fondaparinux 2.5mg s/c once daily** at 6pm should be continued for up to a maximum of 8 doses in total. **Note:** fondaparinux should usually be stopped after successful revascularisation (PCI) unless otherwise directed by Cardiology Consultant. Fondaparinux should not be given to patients who have an indication for full anticoagulation (see above for alternatives) or with concurrent oral anticoagulation if continued.

*If a patient has a true hypersensitivity to aspirin, ticagrelor or fondaparinux, they should be discussed with the cardiologist on call. Other treatment should be administered as above.

**Note patients with body weight <50kg are at increased risk of bleeding.

***Note that in patients with a history of TIA (transient ischaemic attack) or CVA (cerebrovascular accident or stroke) it may be more appropriate to prescribe clopidogrel 75mg daily monotherapy (to cover both secondary prevention of CVA and ischaemic heart disease) after 12 months of aspirin and ticagrelor therapy (with both these agents stopping after 12 months).

It should be noted that currently national advice requires that the ambulance paramedics administer 300mg of clopidogrel and 300mg of aspirin. These patients would then subsequently have to be loaded with ticagrelor on admission to hospital. The data from the PLATO study suggests that patients already loaded with clopidogrel are not at a higher risk of major and minor bleeding events if they then receive ticagrelor, compared to a patient who doesn't receive open label clopidogrel [7].

Consideration of secondary prevention (prescribe as appropriate):

- Consideration of appropriate cholesterol lowering therapy (see local Lipid Management Guidelines)
- If patient has moderate or severe left ventricular systolic dysfunction (LVSD) shown on echocardiogram, prescribers should also refer to the NHS Grampian Medical Treatment Guidelines for Chronic Heart Failure (CHF) due to Left Ventricular Systolic Dysfunction (LVSD) for additional recommendations.
- Use of appropriate anti-ischaemic or antihypertensive therapy in line with current guideline recommendations [(2)] to reduce their cardiovascular risk.

For further information see References (Section 3) and Appendix 1 & 2.

3. References

1) SmPC for fondaparinux and ticagrelor– see http://www.medicines.org.uk
2) European Society of Cardiology Guidelines for the Management of Acute Coronary Syndromes, 2023. (2023 ESC Guidelines for the management of acute coronary syndromes | European Heart Journal | Oxford Academic (oup.com))
3) SIGN 148: Acute Coronary Syndromes, April 2016 (https://www.sign.ac.uk/media/1084/sign148.pdf)
4) Valgimigli et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*, Volume 39, Issue 3, 14 January 2018, Pages 213–260. (https://academic.oup.com/eurheartj/article/39/3/213/4095043)
5) NICE CG 94 (http://www.nice.org.uk/guidance/cg94)
6) The place of fondaparinux in the ESC and ACC/AHA guidelines for anticoagulation in patients with non-ST elevation acute coronary syndromes European Heart Journal Supplements (2008) 10 (Supplement C), C22–C29.
7) Becker et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial European Heart Journal (2011) 32, 2933–2944.

4. Distribution List

All Hospital Consultants, Nurse Managers, Clinical Pharmacists, Lead for Non-Medical Prescribers, Community Hospital Practitioners

5. Responsibilities for Implementation

Organisational:	Chief Executive and Management Teams
Corporate:	Senior Managers
Departmental:	Heads of Service/Clinical Leads
Area:	Line Managers

Hospital/Interface services:	Group Clinical Directors
Operational Management Unit:	Unit Operational Managers

Appendix 1: Fondaparinux 2.5mg/0.5mL Solution For Injection

Also see SmPC - http://www.medicines.org.uk/emc/medicine/29207
Pre-filled syringe containing 2.5mg (0.5mL) of fondaparinux sodium.

Indication:

Treatment of unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) in patients for whom urgent (<120 minutes) invasive management (PCI) is not indicated.

Recommended dosage for adults:

2.5mg subcutaneously once daily at 6pm.
This should be discontinued if 12-hour troponin is negative.

Contraindications:

- Patient attending the cardiac catheterisation laboratory for urgent PCI.
- Patients with CrCl < 20mL/min. In these patients intravenous heparin infusion (25,000units in 50mLs) should be used and adjusted according to the activated partial thromboplastin time ratio (APTTr) (see separate protocol).
- Hypersensitivity to fondaparinux or any excipients.
- The needle shield of the pre-filled syringe may contain dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.
- NSTEMI patients to undergo CABG within 24 hours.
- Patients under the age of 17 years.
- Active signs of bleeding.
- Pregnancy or Lactation.

Cautions:

- Severe hepatic impairment.
- Patients with body weight < 50kg are at increased risk of bleeding.
- Patients with a history of heparin induced thrombocytopenia (HIT).
- Elderly/frail patients (increased bleeding risk).
- Patients with an increased risk of haemorrhage.
- Patients being treated concomitantly with any agents that may increase risk of haemorrhage (e.g. glycoprotein IIa/IIIb inhibitors or thrombolytics).

Administration:

Do not expel the air bubble prior to administration. Administer subcutaneously and ensure that the whole length of the needle is inserted perpendicularly into a skin fold between the thumb and forefinger.

Length of treatment:

Discontinue fondaparinux if 12-hour troponin is negative, following successful revascularisation, at discharge or after 8 doses whichever is sooner.

Side Effects:

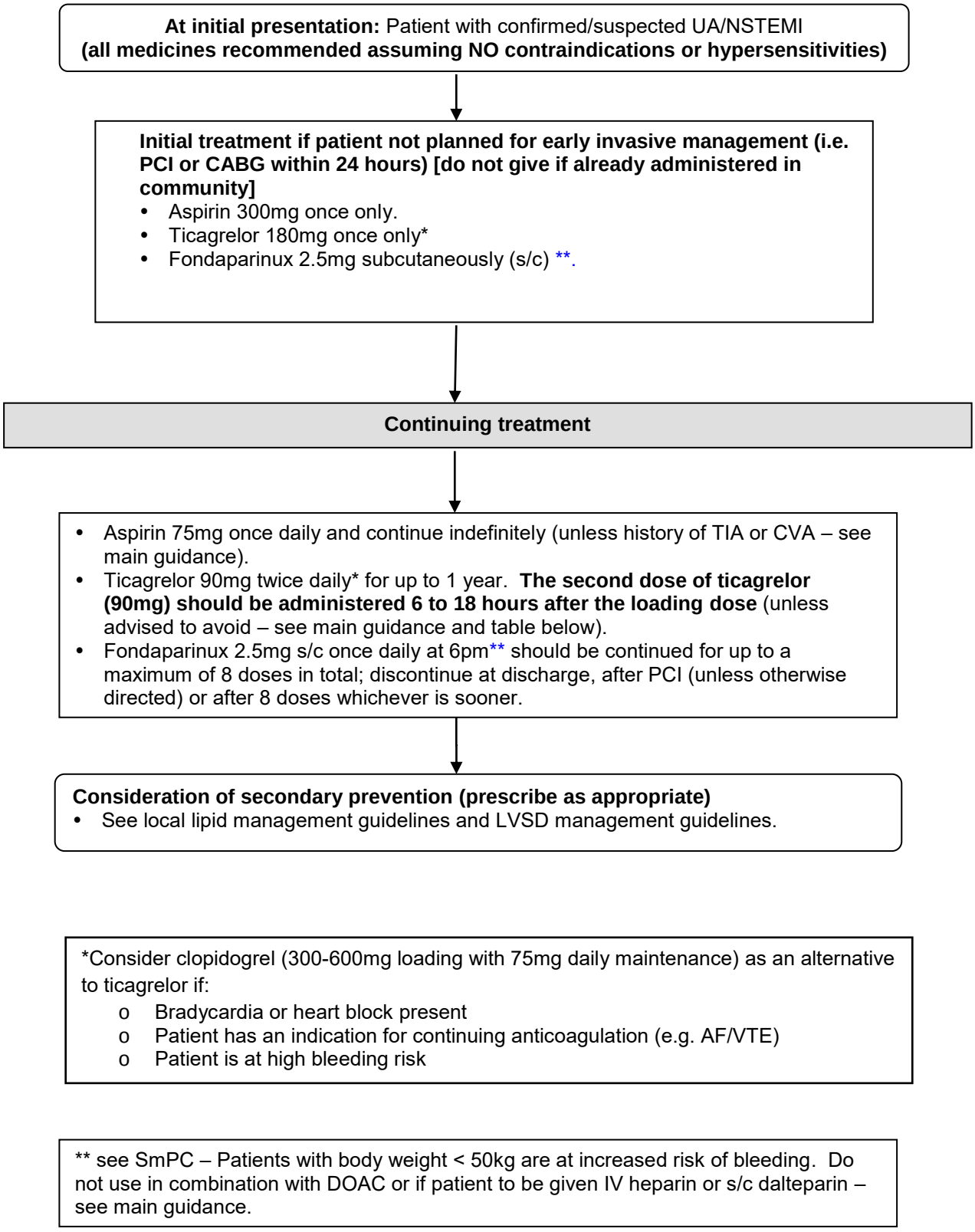
- Bleeding (patient should be monitored for signs of bleeding).
- Increase in hepatic enzymes.
- Rash.
- Pruritis.
- Hypokalaemia.
- GI effects including nausea, vomiting, diarrhoea, constipation, abdominal pain.

Additional notes:

Contains less that 1mmol sodium per dose.

Not for intramuscular injection.

Appendix 2: Flowchart: In-Hospital Management Of Unstable Angina/NSTEMI



*Consider clopidogrel (300-600mg loading with 75mg daily maintenance) as an alternative to ticagrelor if:

- Bradycardia or heart block present
- Patient has an indication for continuing anticoagulation (e.g. AF/VTE)
- Patient is at high bleeding risk

** see SmPC – Patients with body weight < 50kg are at increased risk of bleeding. Do not use in combination with DOAC or if patient to be given IV heparin or s/c dalteparin – see main guidance.